Parkinson-linked genes and toxins that affect neuronal cell death through the Bcl-2 family.

Journal: Antioxid Redox Signal

Publication Year: 2009

Authors: Douglas W Ethell, Qingyan Fei

PubMed link: 18715146

Funding Grants: ES-Derived Cells for the Treatment of Alzheimer's Disease

Public Summary:

Scientific Abstract:
Parkinson's disease (PD) results from the death of specific neuronal populations in the CNS. Potential causative factors include environmental toxins and gene mutations that can combine to dysregulate the processing and degradation of alpha-synuclein. Oxidative stress induced by the neurotoxins MPTP, paraquat, maneb, and rotenone causes lipid peroxidation and protein misfolding that affects cell death through members of the Bcl-2 family. Sufficient activation of Bax and Bak facilitates mitochondrial outer-membrane permeabilization, which releases death-inducing factors that cause apoptotic and nonapoptotic programmed cell death. The formation of alpha-synuclein aggregates is a defining pathologic feature of PD and is induced by these neurotoxins as well as several Parkinson-linked familial mutations. Of the familial mutations identified thus far, two of the loci encode proteins associated with ubiquitin-proteasome degradation of misfolded proteins (Parkin and Uch-L1), and two encode proteins associated with mitochondria and oxidative stress (DJ-1 and PINK1). Both gene and toxin findings indicate that dopaminergic neuron losses in PD are the result of oxidative stress affecting mitochondria function and ubiquitin-proteasome activity. Here we describe how related cell death mechanisms are involved in the pathophysiology of Parkinson's disease.